

Low Dose Ketamine as an Adjunct to Opiates for Acute Pain in the Emergency Department

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Abstract

The overarching question is whether non-sedating doses of ketamine can be utilized in the ED for treatment of acute migraine. This research study will be a prospective, randomized, double-blind, placebo-controlled trial. Because ketamine has yet to be directly studied as treatment for acute migraine headache in the ED, the research team is initially interested if ketamine can reduce pain scores in headache patients and reduce the incidence of recurrence while exhibiting an adequate safety profile. By using a placebo-controlled study design, we can adequately investigate the effectiveness of the medication in a subgroup previously not well studied. The use of a short rescue time period allows us to rapidly provide known effective therapies if necessary.

We propose enrollment of patients upon or shortly after presentation to the emergency department for treatment with ketamine or placebo. After 30 minutes rescue medication in the form of metoclopramide and diphenhydramine will be administered if requested by the patient. Pain scores will be documented using the Numerical rating scale (NRS-11), 4-Point Pain Intensity Categorical Scale, and 4-Point Functional Disability Scale at 0 minutes, 30 minutes, and 60 minutes post treatment. Follow-up telephone calls will be made 72-120 hours after treatment to assess the incidence of recurrence of head pain and patient satisfaction with the treatment.

Subjects eligible for this study must present to the ED with a chief complaint of primary headache that is determined non-emergent by the treating physician.

The following inclusion criteria is in accordance with the International Headache Society (IHS) Clinical Trials Subcommittee for guidelines for controlled trials in migraine:

- (1) Patients ages 18-65
- (2) Meet IHS criteria for
 - (a) Migraine
 - (b) Migraine with aura
 - (c) Probable migraine with or without aura

Upon block randomization, each subject will receive an intravenous dose of 0.2 mg/kg of ketamine or an equivalent volume of saline. After 30 minutes patients will be asked if they need rescue medication, and the treating physician will administer rescue treatment, if requested.

The primary outcome will be achievement of pain response at 30 minutes. Achievement of pain response will be defined as reduction in baseline pain score by at least 50% on the NRS scale.

Secondary outcomes will include attainment of pain-free state, patient headache relief, recurrence of headache, recovery of functional disability, and need for rescue medication.

Background

Migraine and severe headache are prevalent health burdens in the United States adult population. According to a recent statistical compilation of migraine and severe headache prevalence in the United States by Burch et al., migraine or severe headache affects approximately one out of seven Americans each year. In 2012, the three-month age adjusted prevalence of migraine in females was 19.1% and in males 9.0%, with a female to male ratio of 2.17. Many of these migraine sufferers visit a US emergency department (ED) to alleviate painful and debilitating symptoms. During 2009-2010, headache or pain in the head accounted for 3.1% of all ED visits, representing the fourth leading cause of visits to the ED.¹

Due to the high volume of migraine and severe headache related visits in US emergency departments, numerous treatment options are used to various effect to relieve symptoms associated with these painful neurological conditions. The goals of acute migraine treatment are uniform, however, according to the US Headache Consortium, these include treating attacks rapidly and consistently without recurrence, restoring the patient's ability to function, minimizing the use of back-up or rescue medications, being cost effective, and having minimal or no adverse affects.² There is no widely accepted guideline or ideal regimen for the treatment of headache in the emergency department nor is there strong evidence of a single treatment that effectively resolves pain and decreases the incidence of recurring headaches after ED discharge.

Triptans are serotonin analogues that are specifically designed for acute migraine treatment and are recommended as "abortives," meaning they should be taken when the headache is starting. An additional consideration regarding the use of triptans is that patients often present to the ED well outside the time frame in which abortives may be helpful. Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used for acute migraine relief, including sodium naproxen, ibuprofen, and aspirin. However, due to potential gastrointestinal side effects from overuse, NSAIDs may not be the optimal treatment option for patients suffering frequent migraines. Dopamine antagonists have been successful in treating acute migraine and are used for pain relief alone or as an adjunct for nausea. Physicians must be wary of potential side effects from these medications including dystonic reactions, Parkinsonism, and galactorrhea.³ The most controversial treatment option for acute migraine includes opiates. Opiates are considered a non-preferred therapy for acute migraine, and their use should be limited due to potential migraine recurrence and abuse according to the US Headache Consortium.^{4,5} In addition, triptan, NSAID, and opiate use has been shown to induce migraine progression in patients with high migraine frequency (experiencing migraine at least fourteen days per month).^{6,7}

66% of patients treated with sumatriptan had pain persisting at 48 hours. 25% of patients treated with prochlorperazine and 10% of patients treated with octreotide experienced recurring headaches at 48-72 hours. Central sensitization may play a role in headache recurrence and has been observed in patients with various types of headaches.⁸ This implies that over time the stimulus needed to create a nociceptive response decreases while the reported level of perceived pain increases. Patients with chronic migraine or chronic tension headache were shown to have a

higher cumulative pain score in response to pin prick compared to control (54.76 ± 62.9 versus 19.08 ± 21.6 , $p < 0.005$).⁸ The NMDA receptor plays an integral role in the process of central sensitization and ketamine's action on the NMDA receptor has been shown to reduce central sensitization and the wind-up of nociceptive responses.^{9,10}

Recently, investigators have explored drugs commonly used for sedation or anesthesia as potential migraine treatments, including propofol and valproate. Efficacies of these sedative or anesthetic drugs as acute migraine treatment vary, however. A randomized trial comparing valproate, ketorolac, and metoclopramide determined that valproate was not superior in acute migraine relief compared to metoclopramide and ketorolac.¹¹ Clearly, more investigation is needed to study the effectiveness of sedative or anesthetic drugs for the treatment of acute migraine in order to expand treatment options.

Ketamine, a noncompetitive n-methyl-D-aspartate (NMDA) receptor antagonist, is a rapidly acting dissociative amnestic. Although this drug has traditionally been used for procedural sedation and anesthesia, particularly in pediatric populations, ketamine demonstrates hypoalgesic effects on high intensity nociceptive stimuli in humans¹², which has prompted its recent use in pain management. Visser et al. conducted a comprehensive review of ketamine's role in pain management and determined that sub-dissociative doses of ketamine (<1.0 mg/kg) exhibit anti-hyperalgesic and anti-allodynic properties without inducing sedation or dissociative effects.¹³

Additionally, sub-dissociative doses of ketamine administered perioperatively have been shown to reduce pain intensity, morphine consumption twenty four hours post-surgery, and postoperative nausea and vomiting with minimal side effects.¹⁴ In the ED setting, low-dose ketamine proved to be an effective analgesic adjunct to morphine for the treatment of acute pain, though effective dosing is in need of further investigation. While lightheadedness, dysphoria, and dizziness were reported in some patients, no major side effects were observed with this particular use of ketamine in the ED.¹⁵

To date, there are no published studies regarding the use of ketamine specifically for treatment of acute migraine headache. Prior studies describing the use of ketamine for pain often exclude headache patients. When excluded, though, these patients are not the primary focus of the studies and therefore are not present in large numbers. Historically, physicians have been wary to administer ketamine due to fears that this drug increases intracranial pressure in certain populations of patients. A recent review highlights the fact that ketamine does not negatively affect intracranial pressure or cerebral perfusion pressure.¹⁶ Current research suggests that ketamine may have a neuroprotective effect by blocking NMDA-mediated neuron death.¹⁷ In addition, these doses at which there has been concern are significantly higher than those used for analgesia. Because evidence supports ketamine's analgesic properties with minimal side effects, it is proposed that sub-dissociative intravenous ketamine could be an effective acute migraine treatment in US emergency departments.

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> · Age 18-65 · Chief complaint of headache · ICHD of migraine or probable migraine with or without aura* · Provider determination of non-emergent cause 	<ul style="list-style-type: none"> · Over the age of 50 with first time headache · Known adverse reaction or intolerance to study medications · Headache due to trauma · New onset focal abnormal neurologic findings · Active psychotic symptoms · Altered mental status · Provider intends to perform a lumbar puncture · Pregnancy · Breast feeding · Previous enrollment in the study · Fever greater than 100.3°F · Physiologic instability (defined as blood pressure less than 90/50 or greater than 170/100, heart rate below 50 or above 120, or chronic respiratory, renal or hepatic failure) · Suspected cardiac pain

Inclusion/exclusion criteria were determined by the investigators to exclude groups who may be harmed by the administration of any of the study medications (physiological compromise, sensitivity to study medications, patients with headache or chest pain, pregnant females).

Potential subjects will be identified according to the first two inclusion criteria by triage nurses upon arrival in the emergency department. The triage nurses will also use the first exclusion criterion in their decision to contact the research coordinator. The research coordinator will then approach the potential subjects with the following statement:

“We are doing research trying to improve headache pain for patients in the emergency department. You are eligible to be included in this study. Are you interested in learning more about this study and would you consider being involved? If you are not interested, you will still receive medication for pain. If you are interested, we will talk to you more about the study.”

This statement will be further explained as necessary to ensure understanding by the potential subject. If the potential subject is interested in participating in the study, eligibility will be determined by discussion of the exclusion criteria as well as clinical observation. For eligible, interested subjects, informed consent will take place.

Once the protocol is triggered, the study will be explained to potential subjects, including the differences between study arms. The potential risks and benefits will be explained and provided in writing.

Research Procedures

This research study will be a prospective, randomized, double-blind, placebo-controlled trial. After patient recruitment and screening is completed, the on-site investigator will acquire a

signed consent form from each subject. The investigator will then collect demographic data including gender, ethnicity, and age as well as baseline data including duration of headache, previous medications taken, baseline numerical pain score, baseline categorical pain score, functional disability score, presence of aura, and presence of any adverse events including nausea and vomiting.

After baseline data is collected, block randomization will be conducted in conjunction with the pharmacy department to determine whether subjects receive ketamine or placebo. Various studies investigating sub-dissociative ketamine for acute pain in the ED have used intravenous dosages varying from 0.15—3.0 mg/kg.^{15, 20} This study will utilize a 0.2 mg/kg intravenous dose of ketamine or an equivalent volume of saline. Sub-dissociative or “sub-anesthetic” doses of ketamine are reported as doses under 1.0mg/kg and have been shown to provide effective analgesia with few instances of sedation reported.¹⁵ The commonality of placebo-controls in headache treatment studies, trials in the emergency department, and trials in other fields of medicine make this study design an effective metric of ketamine’s efficacy in headache treatment.²¹⁻³⁰

Administration of treatment will be considered time 0 (t=0). The investigator will conduct a standardized questionnaire at 30 minutes post-treatment and 60 minutes post-treatment including the following categories:

- (1) Standard numerical 11-point verbal pain score from 0 to 10
- (2) Categorical pain intensity score from 0 to 4 (0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache)
- (3) Functional disability score from 0 to 3 (0=no disruption of daily activities, 1=performance of daily activities mildly impaired, 2= performance of daily activities moderately impaired, 3=performance of daily activities severely impaired)
- (4) Side effects rating scale for dissociative anesthetics (SERSDA)³¹ including fatigue, dizziness, nausea, headache, feeling of unreality, changes in hearing, changes in vision, mood change, generalized discomfort, and hallucination scored from 0 to 4 (0=no change, 1=weak, 2=modest, 3=bothersome, 4=very bothersome)
- (5) Level of sedation based on Ramsay Sedation Scale (score>2=sedation)²⁰

At t=30, patients will be asked if they would like to receive rescue medication. Rescue treatment will be ordered by the treating physician in a tiered format with the first choice being metoclopramide/diphenhydramine, the second choice being prochlorperazine, and the third choice left to the physician’s discretion. Literature has shown both metoclopramide with diphenhydramine and prochlorperazine with diphenhydramine are equally effective treatments for acute migraine and are commonly used treatments in the CRMH emergency department.¹⁹ After pain scores and side effect data are collected again at t=60, patients will be asked about their satisfaction of treatment and if they would prefer the same treatment again. 72-120 hours after the initial treatment, a blinded research associate will make follow-up calls to each patient.

During the follow up call, the patient will be asked whether they have experienced a new headache since they were discharged, if they have experienced any adverse effects from treatment, an approximate rating of pain at 24 hours after treatment, their current level of pain,

whether they have needed to use additional medications, and if they would prefer to receive this treatment if they were to return to the ED.

Benefits

This study may or may not benefit individual subjects. It is unknown if the study intervention is effective in reducing headache pain and recurrence. There will be no monetary benefit to patients in either arm of the study, nor will patients' clinical care be expedited compared to patients with similar conditions who are not in the study. The benefit to the medical community and of scientific knowledge gained may be great. This study may help further define methods of treatment of acute migraine headache. This may give ED physicians more treatment options for patients who present with migraine headache and may not tolerate standard of care medications. Risks of ketamine are low and transient when given in doses proposed in the study, and the benefit of pain control for the patients and addition of knowledge to medical care are believed to outweigh these risks.

Risks

Side effects to ketamine are infrequent and typically mild. Should a study subject demonstrate symptoms or sign of an adverse medication effect, treatment will be provided as appropriate for the effect.

Should any adverse outcome or injury occur, other than a short-term medication side effect, that is a direct consequence of the investigation, the investigators will reach mutually acceptable agreements with the participant(s) which may include waiver of professional charges or other medical charges in unique circumstances. Should there be any question of injury, individual cases will be reviewed to ascertain any causal injury.

The PI and research coordinator will be primarily responsible for data and safety monitoring. Quality control will include regular data verification and protocol compliance checks. Adverse events and/or protocol deviations will be reported by the PI to the Carilion Institutional Review Board, and if necessary, the FDA, within 24 hours using the Board's established policies and forms. Reports will be made using the Carilion Clinic IRB Unanticipated Problem/Adverse Event Form. These events will be reviewed by the key personnel in conjunction with the IRB and the recommendations will be heeded with regard to the appropriate response to any such event. If any protocol changes are needed, the PI will submit a modification request to the IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change following implementation.

Statistical Considerations

This study has two primary research questions and outcomes: Do patients who receive ketamine experience greater pain relief within 30 minutes and do patients who receive ketamine

experience lower headache recurrence rates within 72 hours. These questions and outcomes are equally important, so the study has been powered to address both of them.

The sample size for this study was calculated based on the number of patients needed for the second arm of this study investigating recurrence of migraine headache after treatment with ketamine or metoclopramide/diphenhydramine. It is estimated that there will be a 50% headache recurrence rate in patients treated with metoclopramide³² and a 30% headache recurrence rate in patients treated with ketamine based on a study investigating tramadol and headache recurrence.¹⁸ With an alpha value of 0.05 and 80% power, it was determined that 54 patients per treatment group were needed in the second arm of this study for a total of 108 patients. However, it is estimated that 20% of patients treated with ketamine will require rescue medication based on a previous study in which ketamine was used to treat acute pain in the ED.³³ In order to obtain 54 patients that receive only ketamine and no rescue medication, this sample size must be increased to 68 subjects per arm for a total of 136 patients. Other outcomes and analyses will be conducted using appropriate statistical techniques but will be considered exploratory/descriptive as it relates to statistical power.